Environmental Science & Technology

pubs.acs.org/est

Article

Cardiopulmonary Mortality and Fine Particulate Air Pollution by Species and Source in a National U.S. Cohort

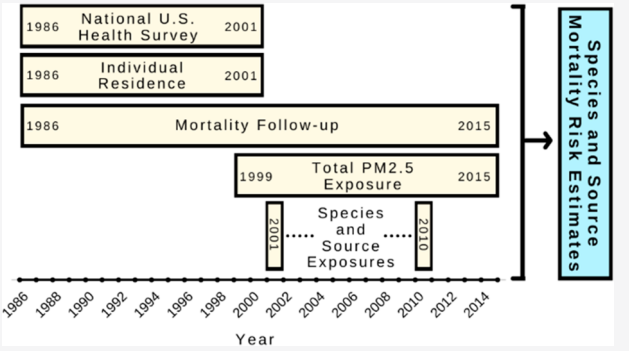
Zachari A. Pond, Carlos S. Hernandez, Peter J. Adams, Spyros N. Pandis, George R. Garcia, Allen L. Robinson, Julian D. Marshall, Richard Burnett, Ksakousti Skyllakou, Pablo Garcia Rivera, Eleni Karnezi, Carver J. Coleman, and C. Arden Pope, III*

Cite This: *Environ. Sci. Technol.* 2022, 56, 7214−7223

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The purpose of this study was to estimate cardiopulmonary mortality associations for long-term exposure to $PM_{2.5}$ species and sources (i.e., components) within the U.S. National Health Interview Survey cohort. Exposures were estimated through a chemical transport model for six species (i.e., elemental carbon (EC), primary organic aerosols (POA), secondary organic aerosols (SOA), sulfate (SO_4), ammonium (NH_4), nitrate (NO_3)) and five sources of $PM_{2.5}$ (i.e., vehicles, electricity-generating units (EGU), non-EGU industrial sources, biogenic sources (bio), "other" sources). In single-pollutant models, we found positive, significant ($p < 0.05$) mortality associations for all components, except POA. After adjusting for remaining $PM_{2.5}$ (total $PM_{2.5}$ minus component), we found significant mortality associations for EC (hazard ratio (HR) = 1.36; 95% CI [1.12, 1.64]), SOA (HR = 1.11; 95% CI [1.05, 1.17]), and vehicle sources (HR = 1.06; 95% CI [1.03, 1.10]). HRs for EC, SOA, and vehicle sources were significantly larger in comparison to those for remaining $PM_{2.5}$ (per unit $\mu g/m^3$). Our findings suggest that cardiopulmonary mortality associations vary by species and source, with evidence that EC, SOA, and vehicle sources are important contributors to the $PM_{2.5}$ mortality relationship. With further validation, these findings could facilitate targeted pollution regulations that more efficiently reduce air pollution mortality.



KEYWORDS: *air pollution, cardiopulmonary mortality, species, source, cohort study*

INTRODUCTION

Air pollution has been estimated as the fourth largest contributor to the global burden of disease.[1] Specifically, cardiopulmonary mortality has consistently been associated with fine particulate air pollution ($PM_{2.5}$).[2−4] $PM_{2.5}$ is comprised of a complex mixture of chemical species, each potentially having different effects on mortality. Mortality associations have also been found to vary across $PM_{2.5}$ sources,[5,6] which could be driven by differences in particle mass, number, size, shape, surface area, or chemical composition. Thus, targeting relatively harmful components (i.e., species or sources) may be more beneficial than simply reducing total $PM_{2.5}$. Current regulations, however, focus on total $PM_{2.5}$, in part due to the uncertainty of component-specific toxicities.

Despite general interest, a limited number of cohort studies have estimated component-specific mortality associations, in part due to difficulties in modeling exposures. A few early cohort studies estimated mortality relationships for sulfates,[7,8] but only recently has a more comprehensive spectrum of species and sources been considered.[5,9] Moreover, the results of past studies have been somewhat inconsistent, establishing the need for additional analysis.

The purpose of this study was to estimate component-specific mortality associations for long-term exposure to $PM_{2.5}$ species and sources. Speciated and source-apportioned $PM_{2.5}$ exposure estimates were linked to a cohort of >160000 adults living in metropolitan statistical areas (MSAs) across the U.S. Within this cohort, cardiopulmonary mortality associations were estimated for six chemical species (i.e., elemental carbon (EC), primary organic aerosols (POA), secondary organic aerosols (SOA), sulfates (SO_4), ammonium (NH_4), and nitrates (NO_3)) and five sources of $PM_{2.5}$ (i.e., vehicles, electricity-generating units (EGU)], non-EGU industrial sources, biogenic sources (bio), and "other" sources). A

Special Issue: Urban Air Pollution and Human Health

Received: June 23, 2021
Revised: September 1, 2021
Accepted: October 5, 2021
Published: October 23, 2021

secondary aim of this analysis was to determine if cardiopulmonary mortality associations differ between primary (i.e., fine particles emitted directly from sources) and secondary $PM_{2.5}$ (i.e., fine particles formed from atmospheric oxidation of gaseous precursors). As such, we separated primary (i.e., EC and POA) and secondary species (i.e., SOA, SO_4, NH_4, and NO_3) within $PM_{2.5}$ sources to estimate relative mortality associations.

METHODS

Study Population Data. For this analysis, a cohort was constructed of adults who participated in the U.S. National Health Interview Survey (NHIS). The NHIS is an annual cross-sectional survey that provides a representative sample of the civilian noninstitutionalized U.S. population. NHIS data are collected continuously throughout each survey year by the U.S. Census Bureau through in-person and telephone interviews. Public use NHIS survey data from 1986 to 2001 were linked to the National Death Index, providing mortality follow-up through December 31, 2015. A detailed description of NHIS sample design, interview procedures, and data access can be found elsewhere.[10,11]

Several exclusion criteria limited the size and determined the composition of the analytic cohort. Merging individuals to exposure estimates required residential data, which were available only at the MSA level and for individuals surveyed before 2002 (n = 587100 remaining). Limited smoking and BMI data further reduced cohort size (n = 198955 remaining), resulting in the exclusion of anyone surveyed in 1986, 1989, or 1996. Individuals missing information on any other covariate were also excluded. After exclusions, the analytic cohort consisted of 164291 adults living within NHIS-sampled MSAs.

Air Pollution Data. Exposure estimates for $PM_{2.5}$ species and sources were developed via a blending of simulated and empirical data. Speciated and source-apportioned concentrations for 2001 and 2010 were derived from chemical transport model (CTM) simulations, with bias corrections to better match speciated monitor data.

A brief description of the CTM simulations follows, with details documented elsewhere.[12] We used the PMCAMx model[13−16] and the "source tagging" algorithm PSAT[17−21] to estimate species and source concentrations. PMCAMx simulates chemical reactions in the gas, aqueous, and particulate phases, with an advanced treatment of organic $PM_{2.5}$ that accounts for the semivolatile nature of primary organic emissions and incorporates recent advances in secondary organic PM chemistry.[22−24] Simulations were performed using an internally consistent set of 2001 and 2010 emissions inventories, developed by Xing et al.[25] Emissions inventories were constructed from several activity and emission control databases, including the State Energy Data System, National Emissions Inventory trends report, and 2011 National Transportation Statistics.[25] Meteorological data used in PMCAMx were taken from simulations performed with the Weather Research Forecasting model (WRF v3.6.1).

The PMCAMx model domain covered the continental United States at a horizontal resolution of 36 km. While coarse, a 36 km resolution was necessary to maintain computational feasibility. Additionally, increasing simulation resolution from 36 × 36 to 1 × 1 km grids in a major city (i.e., Pittsburgh) had minimal effect on predicted exposures (less than 3%).[26]

Species predicted by the model and used in the health analysis included EC, POA, SOA, SO_4, NH_4, and NO_3. These species were selected as they are major contributors to total $PM_{2.5}$ and were reliably estimated. Concentrations of sodium, chloride, and mineral dust were also estimated but not used in the health analysis due to low concentrations or lack of speciated monitor data.

Source categories were necessarily identical to those from the emissions inventories used as inputs to the CTM.[25] While $PM_{2.5}$ source categories could be defined in a variety of ways, the categories used in this study reflect sources that have traditionally been most relevant for regulatory purposes. The EGU category represents emissions from electricity-generating units included in the U.S. Environmental Protection Agency's Integrated Planning Model. Non-EGU includes all other industrial point sources. The vehicles category includes emissions from on-road vehicles in the U.S. and off-road vehicles in the entire domain. Biogenic includes emissions from vegetation. The "other" source includes on-road vehicles from Canada and Mexico plus all other emissions.

As with most CTM simulations, the concentrations directly predicted by PMCAMx exhibited systematic regional biases. Therefore, speciated $PM_{2.5}$ concentrations predicted by PMCAMx were adjusted using geographically weighted regression[27] to better match speciated monitor data.[28,29] For each species, a separate regression was used to predict the bias between CTM predictions and observed concentrations. Regression predictor variables included speciated CTM concentrations, inverse distance to nearest urban area, average monitor elevation difference, and local bias between CTM and empirically modeled $PM_{2.5}$. Pollution monitor observations were weighted using a Gaussian function that decays with distance. Bias predictions were made at the census tract level to allow for finer-resolution corrections in areas with higher population density. The CTM fields were then corrected using the predicted biases for each census tract and species. During this process, the fractional source apportionment for individual species was assumed to be constant.[26]

In addition to component-specific exposures, multiple estimates of total $PM_{2.5}$ exposure were used in this analysis. One estimate of total $PM_{2.5}$ exposure was defined as the sum of speciated concentrations (i.e., $PM_{2.5}$ CTM '01, '10). An additional estimate of $PM_{2.5}$ exposure (i.e., $PM_{2.5}$ IEG '01, '10) was predicted using an integrated empirical geographic (IEG) model, which applies pollution monitor measurements within a universal kriging framework.[30] While many IEG model inputs were temporally fixed, year-to-year trends and variations were accounted for through temporally variable land use data and satellite-derived pollution estimates.[30]

Census tract level exposure estimates for $PM_{2.5}$ and components were aggregated to the MSA level as a population-weighted average. Details on how MSA borders were defined in the aggregation process are provided in Appendix A in the Supporting Information. Individual exposures were assigned, on the basis of residence at the time of the survey, as the simple average of 2001 and 2010 MSA-level concentration estimates. To assess the effects of using only two annual concentration estimates, an additional measure of total $PM_{2.5}$ was constructed as the average of annual, IEG-modeled $PM_{2.5}$ from 1999 to 2015 (i.e., $PM_{2.5}$ IEG '99−'15).

Mortality Risk Analysis. Cardiopulmonary mortality associations were quantified as adjusted hazard ratios (HRs) from Cox proportional hazards models (PHREG procedure in SAS, version 9.4; SAS Institute Inc.). Concentration−response

https://doi.org/10.1021/acs.est.1c04176
Environ. Sci. Technol. 2022, 56, 7214−7223

curves were not estimated, as a previous analysis with the NHIS cohort found that the concentration−response relationship between $PM_{2.5}$ and cardiopulmonary mortality was approximately linear.[2]

Cardiopulmonary mortality was defined, in accordance with the tenth revision of the International Classification of Diseases (ICD-10), to include deaths from cardiovascular disease (ICD-10 codes: I00−I09, I11, I13, I20−I51), cerebrovascular disease (I60−I69), chronic lower respiratory disease (J40−J47), and influenza or pneumonia (J09−J18). Causes of death corresponding to the preceding ICD-10 codes are specified in Table S1. For cardiopulmonary mortality, survival times were calculated as the difference between the year of death and the survey year. Otherwise, survival times were censored at the date of noncardiopulmonary mortality or the end of follow-up (i.e., 2015).

Control variables were chosen *a priori* on the basis of past research conducted with the NHIS cohort.[2,31] The following control variables were used in each model. Age, sex, and race−ethnicity were controlled for by allowing each combination of age (one year), sex, and race−ethnicity to be assigned its own baseline hazard (using the STRATA statement of the PHREG procedure in SAS). Models also included categorical variables for family income ($0−35000; $35000−50000; $50000−75000; >$75000), marital status (married, divorced, separated, never married, widowed), educational attainment (less than high school graduate, high school graduate, some college, college graduate, more than college graduate), BMI (<20, 20−25, 25−30, 30−35, >35 kg/m^2), smoking status (current, former, never), census region (Northeast, South, Midwest, West), and survey year. For details on how control variables were harmonized across survey years, see Appendix B in the Supporting Information.

While control variables were consistent across models, specifications differed in how they accounted for relationships among $PM_{2.5}$ components. Single-pollutant models included all control variables along with a single component of $PM_{2.5}$. This approach provides greater statistical power, as it is less affected by multicollinearity, yet it yields inherently biased estimates due to component correlation with total $PM_{2.5}$. Mass-adjusted models addressed this issue by including remaining $PM_{2.5}$ (i.e., CTM predicted total $PM_{2.5}$ minus $PM_{2.5}$ component). Moreover, mass-adjusted models provide a formal structure for estimating the likelihood that mortality associations differ between components. That is, for each component a Wald hypothesis test was conducted, with the null hypothesis that the component and the remaining $PM_{2.5}$ HRs were equivalent.

Mortality associations were also estimated for primary and secondary $PM_{2.5}$, within sources. While several source categories were almost entirely primary or secondary, total $PM_{2.5}$, vehicle sources, and "other" sources had sizable portions of both primary and secondary species. Thus, only total $PM_{2.5}$, vehicle sources, and "other" sources were separated into primary and secondary species. Source-specific primary $PM_{2.5}$ was defined as the sum of EC and POA from a given source, whereas secondary $PM_{2.5}$ was defined as the sum of SOA, SO_4, NH_4, and NO_3. Single-pollutant models were estimated, along with a two-pollutant model that separately included primary and secondary $PM_{2.5}$ from a given source (e.g., primary vehicles and secondary vehicles).

In all cases, pollution exposures were measured in micrograms per cubic meter ($\mu g/m^3$) and modeled as continuous variables. Exposures were scaled such that HRs were relative to either a unit or mean $\mu g/m^3$ increase in exposure. When HRs are scaled per unit they more accurately reflect relative toxicities, especially after adjusting for remaining $PM_{2.5}$. Alternatively, scaling exposures per mean incorporates a component's relative contribution to total $PM_{2.5}$ and accounts for differential scaling bias in single-pollutant models.

RESULTS

Data Summary. Individuals within our cohort were predominantly female (56.6%), white non-Hispanic (66%), married (50.8%), high-school graduates (30.7%), and never smokers (51.7%) (Table 1). Figure S1 maps pollution exposure estimates for $PM_{2.5}$ mass and components across NHIS-surveyed MSAs, displaying the spatial distribution of exposures. Spatial variation for some components (e.g., EGU and SO_4) was mostly regional, which reduced statistical power in controlling for census region. Additionally, Figure 1 depicts the relative species composition of each source. Some sources (e.g., bio) were primarily comprised of a single species (e.g.,

Table 1. Cohort Summary Statistics

characteristic	*n*	percent
full cohort	164291	100.00
cardiopulmonary deaths	13732	8.36
age (mean, std)	44.12	17.14
sex		
female	93015	56.62
male	71276	43.38
race−ethnicity		
black non-Hispanic	25823	15.72
Hispanic	23128	14.08
other/unknown	6892	4.19
white non-Hispanic	108448	66.01
income		
$0−35000	52713	32.09
$35000−50000	23934	14.57
$50000−75000	32689	19.90
$75000 and over	54955	33.45
marital status		
married	83435	50.78
never married	39431	24.00
divorced	20462	12.45
widowed	14529	8.84
separated	6434	3.92
educational attainment		
<high- inrschool graduate	30891	18.80
high-school graduate	50491	30.73
some college	40837	24.86
college graduate	25280	15.39
post-college graduate	16792	10.22
BMI		
<20	14955	9.10
20−25	69175	42.11
25−30	53810	32.75
30−35	18212	11.09
>35	8139	4.95
smoking status		
current	41400	25.20
former	37894	23.07
never	84997	51.74

https://doi.org/10.1021/acs.est.1c04176
Environ. Sci. Technol. 2022, 56, 7214−7223

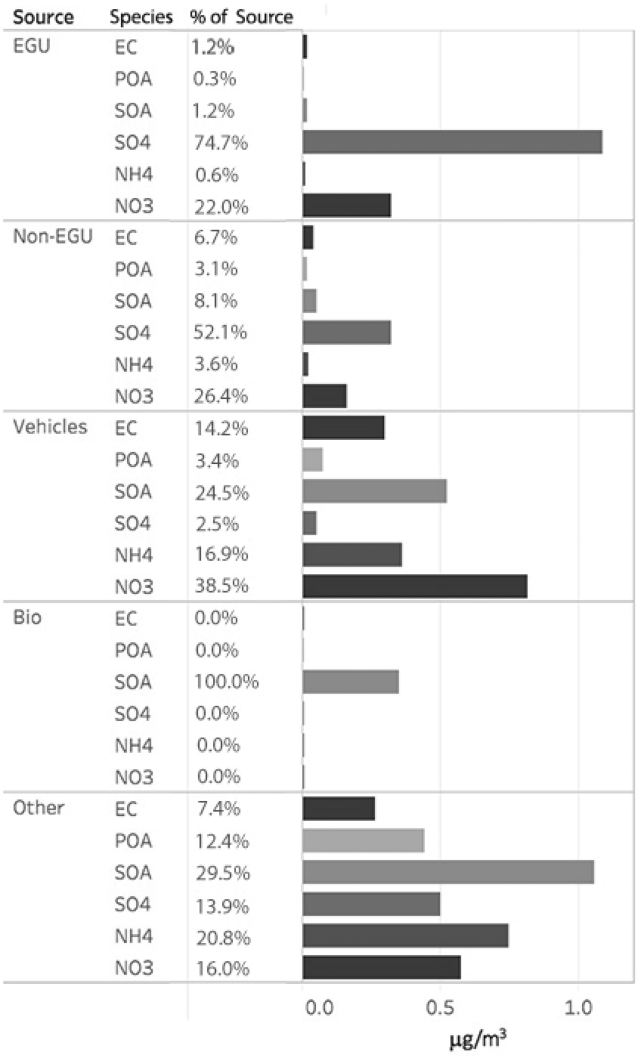


Figure 1. Average species composition within $PM_{2.5}$ sources. Averages were calculated after assigning individual exposures.

SOA), whereas vehicle source $PM_{2.5}$ was a mixture of all species.

Additional exposure summary statistics are provided in Table 2, including means, standard deviations, and pairwise correlations between components. On average, CTM estimates for $PM_{2.5}$ exposure were about 2 $\mu g/m^3$ lower than IEG estimates, as the former did not model species such as road dust and sea salt; nevertheless, all measures of total $PM_{2.5}$ were highly correlated ($r > 0.94$). Correlations were also high between $PM_{2.5}$ components, which presented difficulties in isolating independent mortality associations. Each component was less correlated with remaining $PM_{2.5}$ than with total $PM_{2.5}$, which justified including the former in mass-adjusted models.

Measures of temporal consistency and exposure modeling accuracy for $PM_{2.5}$ components are reported in Table 3. For each component, temporal consistency was assessed in two ways: first, by a comparison of the 2001 and 2010 concentration means, and second, by consideration of the correlation between 2001 and 2010 concentrations. The temporal consistency was relatively low for EC and POA, suggesting that these components may exhibit higher exposure measurement error. Specifically, the within-component correlations between 2001 and 2010 exposures were 0.78 for both EC and POA, while all other component intertemporal correlations were 0.87 or higher. The exposure modeling accuracy was assessed through a 10-fold cross-validation (CV) R^2 comparison of CTM predictions and ground-level monitor data. In general, exposure modeling was more accurate for secondary species. For 2001 exposures, CV R^2 ranged from 0.63 for EC to 0.97 for SO_4.

SO_4 also had the highest CV R^2 for 2010 exposures, whereas organic aerosols were modeled relatively imprecisely (2010 CV $R^2 = 0.50$).

Mortality Risk Analysis. Single-pollutant HRs, per unit $\mu g/m^3$ (panel A) and per relative mean $\mu g/m^3$ (panel B), are displayed in Figure 2. Numerical equivalents of these estimates, along with HRs scaled per interquartile range, are reported in Table S2. In single-pollutant models, there were positive, significant ($p < 0.05$) mortality associations for $PM_{2.5}$ mass and each component, except for POA. Relative effect sizes differed between scaling methods, as each approach answered a distinct question. Scaling HRs per unit provides information about per mass concentration harmfulness, whereas scaling per mean reflects a component's aggregate contribution to mortality risk.

Per unit $\mu g/m^3$ (Figure 2A), single-pollutant HRs were relatively large for EC, non-EGU, and bio. These differences are difficult to interpret due to confounding from correlation with total $PM_{2.5}$. That is, in single-pollutant models components with higher correlation with total $PM_{2.5}$ likely exhibit a larger positive bias. Moreover, this bias is greater for components with lower exposure means (e.g., EC, non-EGU, bio) when estimates are scaled per unit $\mu g/m^3$.

Scaling single-pollutant HRs per mean increase in exposure (panel B) partially accounts for this problem, while allowing estimates to reflect a component's relative contribution to total $PM_{2.5}$ exposure. Of the three estimates of total $PM_{2.5}$ exposure, the 17-year average (i.e., 1999−2015) of IEG-modeled $PM_{2.5}$ was associated with the largest increase in mortality risk (HR = 1.41; 95% CI [1.26, 1.56]; per 11.32 $\mu g/m^3$). Despite having a similar mean exposure, the estimated HR for the two-year average (i.e., 2001 and 2010) of IEG-modeled $PM_{2.5}$ was 26% smaller (HR = 1.30; 95% CI [1.19, 1.43]; per 11.64 $\mu g/m^3$) than that of its 17-year counterpart. This suggests that assigning component exposures as the average of two annual concentrations resulted in conservative mortality risk estimates. Among $PM_{2.5}$ components, EC (HR = 1.27; 95% CI [1.18, 1.37]; per 0.69 $\mu g/m^3$) and SOA (HR = 1.30; 95% CI [1.20, 1.41]; per 2.75 $\mu g/m^3$) had the highest HRs per relative mean increase in exposure.

To account for bias from correlation between component and total $PM_{2.5}$ exposure, Figure 3 plots single-pollutant parameter estimates (i.e., natural log of HR) according to component correlation with $PM_{2.5}$ mass. The plotted diagonal provides a baseline comparison by indicating the effect size one would expect to see solely from component correlation with $PM_{2.5}$ exposure. Thus, the distance from the plotted diagonal serves as a basic metric for whether single-pollutant mortality associations are relatively high or low. As such, Figure 3 provides some indication that EC, SOA, and SO_4 have relatively high single-pollutant associations with cardiopulmonary mortality.

While Figure 3 is useful for interpreting single-pollutant estimates, a more thorough attempt at estimating component-specific mortality associations is to explicitly control for remaining mass. Figure 4 plots HRs from mass-adjusted models, which included a given $PM_{2.5}$ component (black circle

https://doi.org/10.1021/acs.est.1c04176
Environ. Sci. Technol. 2022, 56, 7214−7223

Table 2. Exposure Means, Standard Deviations (SD), and Pearson Correlation Coefficients[a,b]

	$PM_{2.5}$			species						source				
	IEG[c]	IEG[d]	CTM[e]	EC	POA	SOA	SO_4	NH_4	NO_3	EGU	non-EGU	veh.[f]	bio	other
	Mean $\mu g/m^3$ (SD)													
	11.32 (1.93)	11.64 (2.28)	9.75 (2.25)	0.69 (0.20)	0.54 (0.17)	2.75 (0.71)	2.60 (0.92)	1.25 (0.42)	1.92 (0.96)	1.46 (0.90)	0.61 (0.23)	2.12 (0.97)	0.35 (0.16)	3.59 (0.90)
	Correlations													
IEG[c]	1.00													
IEG[d]	0.98	1.00												
CTM[e]	0.95	0.95	1.00											
EC	0.70	0.69	0.72	1.00										
POA	0.41	0.41	0.47	0.75	1.00									
SOA	0.72	0.73	0.79	0.81	0.59	1.00								
SO_4	0.41	0.39	0.39	−0.05	−0.30	−0.12	1.00							
NH_4	0.80	0.80	0.84	0.35	0.11	0.37	0.75	1.00						
NO_3	0.71	0.74	0.77	0.65	0.56	0.78	−0.22	0.45	1.00					
EGU	0.30	0.29	0.31	−0.19	−0.39	−0.20	0.96	0.71	−0.24	1.00				
non-EGU	0.68	0.65	0.60	0.06	−0.11	0.14	0.73	0.80	0.25	0.70	1.00			
veh.[f]	0.73	0.74	0.77	0.86	0.69	0.89	−0.24	0.35	0.91	−0.33	0.08	1.00		
bio	0.55	0.52	0.57	0.35	0.16	0.43	0.55	0.62	0.11	0.54	0.45	0.17	1.00	
other	0.91	0.91	0.97	0.74	0.54	0.81	0.27	0.78	0.81	0.17	0.50	0.80	0.48	1.00
rem. $PM_{2.5}$				0.68	0.41	0.61	−0.02	0.77	0.47	−0.09	0.52	0.47	0.52	0.92

[a]For each component, remaining $PM_{2.5}$ (rem. $PM_{2.5}$) was calculated as total $PM_{2.5}$ mass minus component-specific mass. [b]All statistics were cohort-weighted, as they were calculated after individual-level exposures were assigned. [c]Annual average of 1999 to 2015 IEG modeled $PM_{2.5}$. [d]Annual average of 2001 and 2010 IEG modeled $PM_{2.5}$. [e]Annual average of 2001 and 2010 CTM estimated $PM_{2.5}$. [f]Vehicles.

Table 3. Temporal Consistency[a] and Accuracy[b] of Predicted Exposures

pollutant	'01 '10 corr	'01 mean	'10 mean	'01 CV R^2	'10 CV R^2
$PM_{2.5}$					
IEG	0.70	13.62	9.67		
CTM	0.93	11.56	7.94		
species					
EC	0.78	0.67	0.72	0.63	0.68
POA	0.78	0.66	0.42	0.74	0.50
SOA	0.87	3.21	2.28	0.74	0.50
SO_4	0.92	3.23	1.98	0.97	0.90
NH_4	0.90	1.50	0.99	0.93	0.82
NO_3	0.89	2.29	1.54	0.82	0.83
source					
EGU	0.96	1.95	0.96		
non-EGU	0.97	0.70	0.52		
vehicles	0.98	2.66	1.58		
bio	0.92	0.36	0.35		
other	0.90	4.14	3.03		

[a]Measures of temporal consistency included cohort-weighted annual exposure means (e.g., '01 mean) and Pearson correlation coefficients between 2001 and 2010 exposures (i.e., '01 '10 corr). [b]Exposure accuracy was measured through a 10-fold cross validation (CV) R^2 comparison of predicted concentrations and ground-level monitor observations.

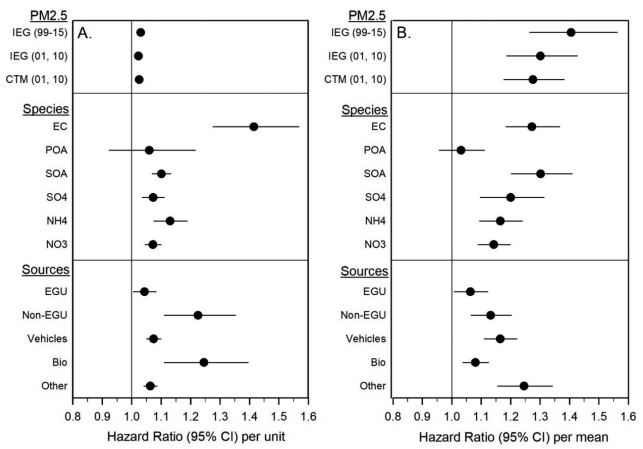


Figure 2. Single-pollutant hazards ratios and 95% confidence intervals (CI) per unit $\mu g/m^3$ (panel A) and per relative mean $\mu g/m^3$ (panel B) increase in exposure.

point estimates) and remaining $PM_{2.5}$ mass (white square point estimates). Estimates are reported per unit $\mu g/m^3$ to reflect relative toxicities. Numerical equivalents of these estimates are provided in Table S3.

For several components, controlling for remaining $PM_{2.5}$ reduced the magnitude of single-pollutant HRs. Specifically, for POA, SO_4, NH_4, EGU, and non-EGU, positive single-pollutant risk estimates became either null or negative after controlling for remaining $PM_{2.5}$. In contrast, EC maintained an elevated HR after controlling for remaining mass (HR = 1.36; 95% CI [1.12, 1.64]; per unit $\mu g/m^3$), with risk estimates 10 times greater than that for total $PM_{2.5}$ (per unit $\mu g/m^3$). Similarly, SOA mortality risk estimates remained large after controlling for remaining mass (HR = 1.11; 95% CI [1.05, 1.17]; per unit $\mu g/m^3$). For $PM_{2.5}$ sources, controlling for remaining mass generally reduced the magnitude of single-pollutant HRs, except for vehicle sources. That is, vehicle source HRs were nearly identical in single-pollutant (HR = 1.07; 95% CI [1.05, 1.10]; per unit $\mu g/m^3$) and mass-adjusted models (HR = 1.06; 95% CI [1.03, 1.10]; per unit $\mu g/m^3$).

In Figure 4, component HRs are plotted adjacent to remaining $PM_{2.5}$ mass HRs to facilitate a comparison of relative

https://doi.org/10.1021/acs.est.1c04176
Environ. Sci. Technol. 2022, 56, 7214−7223

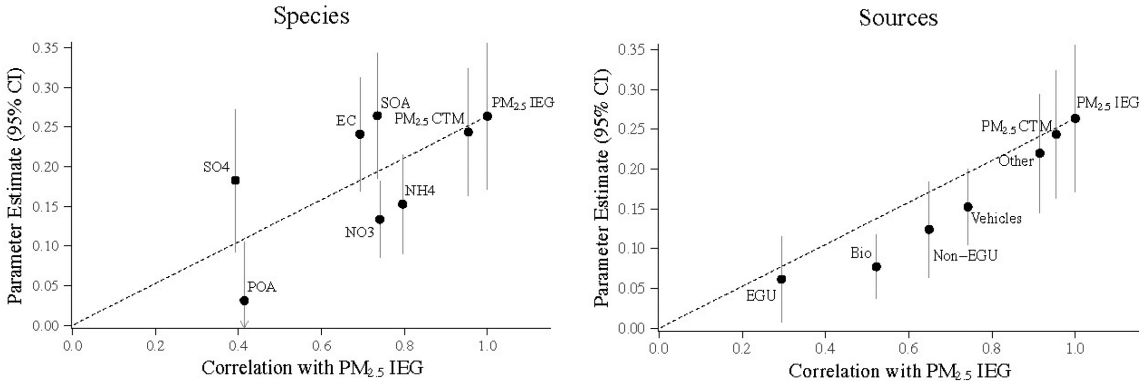


Figure 3. Parameter estimates (i.e., natural log of hazard ratios) and 95% confidence intervals (CI) from single-pollutant models plotted according to component correlation with $PM_{2.5}$ mass. Estimates are relative to a component mean increase in exposure.

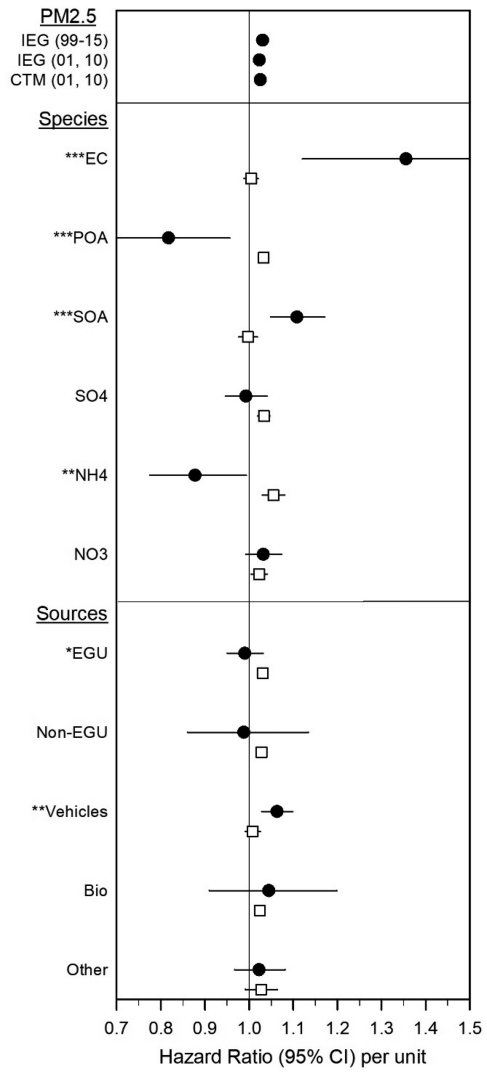


Figure 4. Remaining $PM_{2.5}$ mass adjusted hazard ratios (HRs) and 95% confidence intervals (CI) per unit $\mu g/m^3$. For each component, a separate model was specified to include two pollutants: the component (black circle point estimates) and remaining $PM_{2.5}$ mass (i.e., total $PM_{2.5}$ minus component) (white square point estimates). Asterisks reflect p values from a hypothesis test with the null hypothesis that component and remaining $PM_{2.5}$ HRs were equivalent (*$p < 0.10$; **$p < 0.05$; ***$p < 0.01$).

toxicities. For species, both EC and SOA had higher HRs than their remaining $PM_{2.5}$ mass. A formal hypothesis test revealed that these differences were statistically significant, with p values of 0.004 and 0.005 for EC and SOA, respectively. Source-specific HRs were generally lower than HRs for remaining mass. However, the HR for vehicle source pollution was significantly larger ($p = 0.03$) than its respective remaining mass term.

In addition to component-specific HRs, an aim of this analysis was to estimate mortality associations for primary and secondary $PM_{2.5}$. Figure 5 plots single-pollutant (black point estimates) and two-pollutant HRs (red point estimates) for primary (circle point estimates) and secondary species (diamond point estimates) from total $PM_{2.5}$, vehicles, and "other" sources. Estimates are reported per unit (Figure 5A) and per mean $\mu g/m^3$ (Figure 5B) increase in exposure. Numerical equivalents of these estimates are provided in Table S4.

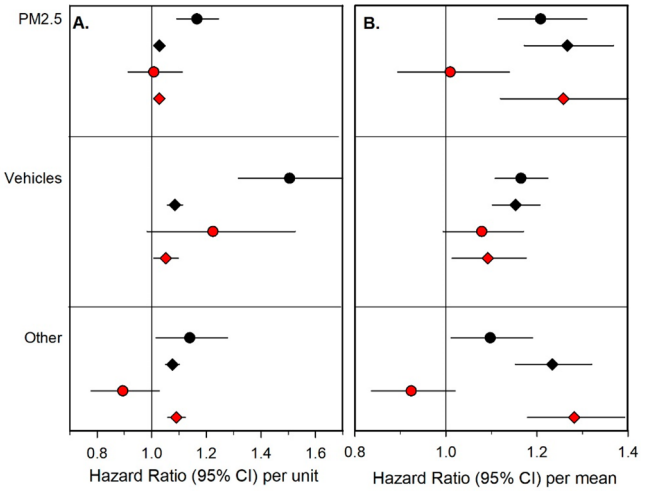


Figure 5. Hazard ratios and 95% confidence intervals (CI) for primary (circle point estimates) and secondary species (diamond point estimates) within $PM_{2.5}$ sources. Single-pollutant models (black point estimates) included one pollutant (e.g., primary vehicles), whereas two-pollutant models (red point estimates) included both primary and secondary species from a given source (e.g., primary vehicles and secondary vehicles). Estimates are reported per unit $\mu g/m^3$ (A) and per mean $\mu g/m^3$ (B) increase in exposure.

https://doi.org/10.1021/acs.est.1c04176
Environ. Sci. Technol. 2022, 56, 7214−7223

Per unit $\mu g/m^3$, single-pollutant HRs were consistently larger for primary species. This was likely due to confounding from correlated components, as the same did not hold in two-pollutant specifications. In two-pollutant models, HRs were similar for total primary and total secondary $PM_{2.5}$, as well as for primary and secondary $PM_{2.5}$ from vehicle sources. For "other" sources, the primary $PM_{2.5}$ HR was significantly smaller, as "other" source primary $PM_{2.5}$ was predominantly POA (see Figure 1).

When they were scaled per mean, HRs for primary and secondary $PM_{2.5}$ from vehicle sources were nearly identical, in both single-pollutant and two-pollutant specifications. In contrast, for total $PM_{2.5}$ and "other" sources, HRs were larger for secondary species. Specifically, in a two-pollutant model, the HR for secondary total $PM_{2.5}$ (HR = 1.26; 95% CI [1.12, 1.41]; per 8.52 $\mu g/m^3$) was significantly larger ($p = 0.05$) than for primary total $PM_{2.5}$ (HR = 1.01; 95% CI [0.89, 1.14]; per 1.23 $\mu g/m^3$). While this can be attributed to higher exposure levels for secondary species, it does suggest that secondary $PM_{2.5}$ contributes more than primary $PM_{2.5}$ to the actualized risk of cardiopulmonary mortality.

Measures of model fit from single-pollutant models, along with two additional specifications that included all species (six pollutants) or all sources (five pollutants) simultaneously, are provided in Table S5. IEG estimates fit mortality outcomes better than CTM estimates of total $PM_{2.5}$ exposure. Single-pollutant models for EC, SOA, and vehicles fit mortality better than both (i.e., IEG and CTM) two-year averages of $PM_{2.5}$, but not the 17-year average of IEG-modeled $PM_{2.5}$. Including all species or all sources separately did not improve the model fit over aggregate $PM_{2.5}$ specifications.

DISCUSSION

In this analysis, there were positive, significant ($p < 0.05$) single-pollutant mortality associations for $PM_{2.5}$ and all components, except for POA. While most associations became insignificant after controlling for remaining $PM_{2.5}$, we found evidence that EC, SOA, and vehicle sources are important contributors to the risk of cardiopulmonary mortality.

Species. Of the considered components, we found that EC was associated with the largest increase in cardiopulmonary mortality risk (per unit $\mu g/m^3$), with and without controlling for remaining $PM_{2.5}$. Moreover, in a mass-adjusted model the HR for EC was significantly larger ($p = 0.004$) than for remaining $PM_{2.5}$ mass.

In past studies, EC has shown elevated single-pollutant mortality associations that lose significance after adjusting for other pollutants.[9,32,33] A previous analysis of the American Cancer Society (ACS) cohort estimated 8 times greater cardiopulmonary mortality risk for EC than for $PM_{2.5}$ in single-pollutant models (per unit $\mu g/m^3$), with EC HRs substantially reduced and insignificant in multipollutant models.[32] Similarly, in the California Teacher's Study (CTS) cohort, Ostro et al.[9] found that significant ($p < 0.05$), single-pollutant EC mortality associations became insignificant after adjusting for NO_3.

Instability in the EC mortality association has been attributed to EC's complex, heterogeneous nature.[9,34] Specifically, high spatial variation presents difficulties in accurately modeling EC exposures. While EC was modeled relatively imprecisely (see Table 3), we observed significant EC HRs in mass-adjusted models, providing some evidence that EC has a direct relationship with cardiopulmonary mortality.

In addition to EC, our results suggest that SOA may be a key contributor to the $PM_{2.5}$ mortality relationship. That is, in a mass-adjusted model the HR for SOA was significantly larger ($p = 0.005$) than for remaining $PM_{2.5}$ (per unit $\mu g/m^3$). Similarly, in the CTS cohort anthropogenic SOA was significantly ($p < 0.05$) associated with ischemic heart disease (IHD) mortality in single-pollutant models.[9] Moreover, they found that mortality associations for anthropogenic SOA in the ultrafine range remained significant in all combinations of two-pollutant models.[9] Short-term analyses have found similar results, with a study in Xi'an, China, reporting significant cardiovascular and respiratory mortality associations for organic carbon, with and without adjusting for $PM_{2.5}$ mass.[35]

While EC and SOA maintained relatively high HRs, single-pollutant mortality associations for SO_4 vanished after controlling for the remaining $PM_{2.5}$, suggesting that SO_4 is, at least in part, a tracer of other harmful pollutants. SO_4, along with its precursor SO_2, has been significantly associated with mortality in several observational cohort studies,[32,36] including some of the earliest to consider speciated $PM_{2.5}$.[7,37] However, the plausibility of a causal link between SO_4 and mortality is not supported by toxicology studies, which collectively report minimal biological potency in humans or animals at environmentally relevant levels.[38] Thus, observational associations could represent the mortality relationship of particulate species and copollutants correlated with SO_4, not SO_4 alone.[32]

Similarly, mortality associations were relatively low for POA and NH_4, as exposures were inversely associated with cardiopulmonary mortality risk in mass-adjusted models. With high correlations between remaining and total $PM_{2.5}$, mass-adjusted HRs could reflect changes in the $PM_{2.5}$ composition, not an aggregate decrease in $PM_{2.5}$ exposure. Specifically, inverse NH_4 and POA mortality associations could represent a decrease in average $PM_{2.5}$ toxicity when the fractional $PM_{2.5}$ composition has larger proportions of these species. Alternatively, inverse NH_4 and POA mortality associations could be the result of statistical noise or some unobserved confounder. In any case, it remains unlikely that exposure to NH_4 or POA decreases risk of cardiopulmonary mortality.

Sources. While each considered source was significantly ($p < 0.05$) associated with mortality in single-pollutant models, only vehicle sources remained significant after adjusting for remaining $PM_{2.5}$ mass. In mass-adjusted models, the estimated increase in cardiopulmonary mortality risk from exposure to vehicle source $PM_{2.5}$ was 8 times greater (per unit $\mu g/m^3$) than that from remaining $PM_{2.5}$ mass. This difference was statistically significant ($p = 0.03$) in a formal hypothesis test for the equality of vehicle source and remaining $PM_{2.5}$ HRs.

Past analyses have supported a relationship between mortality and long-term exposure to vehicle source $PM_{2.5}$, although uncertainty remains due to a limited number of studies.[39] In the CTS cohort, there were statistically significant ($p < 0.05$) single-pollutant associations between IHD mortality and four subgroups of vehicle source $PM_{2.5}$.[9] Short-term analyses have also reported significant associations between adverse health effects and vehicle source $PM_{2.5}$. An analysis in Barcelona, Spain, found that traffic-related $PM_{2.5}$ was associated with a more than 8% increase in daily cardiovascular mortality (per 9.7 $\mu g/m^3$ with 2 day lag), in single- and multiple-source models.[40] Similarly, a U.S. study found that 10 $\mu g/m^3$ of mobile source $PM_{2.5}$ increased daily mortality by 3.4%.[41] In addition to daily mortality, a series of short-term

https://doi.org/10.1021/acs.est.1c04176
Environ. Sci. Technol. 2022, 56, 7214−7223

studies in New York State found that vehicle source $PM_{2.5}$ was significantly associated with hospitalizations and emergency department visits for influenza, cardiac arrythmia, ischemic stroke, and congestive heart failure.[42,43] These studies, combined with the present analysis, provide suggestive evidence that vehicle sources are an important contributor to the $PM_{2.5}$ morbidity and mortality relationship.

Primary vs Secondary. Estimating the relative mortality associations of primary and secondary $PM_{2.5}$ yielded little insight beyond what can be explained by component-specific mortality associations and differences in exposure means. That is, differences in source-specific primary and secondary mortality associations were driven by either the species composition within the source (see Figure 3) or the relative exposure means. Ultimately, our results suggest that mortality associations differ more within primary and secondary designations (e.g., EC vs POA) than between primary and secondary designations (e.g., primary vehicles vs secondary vehicles). Nevertheless, with a significantly larger HR per mean exposure, total secondary $PM_{2.5}$ likely contributes more than total primary $PM_{2.5}$ to the actualized risk of cardiopulmonary mortality.

Limitations. An inherent limitation of observational air pollution analyses is imperfect assignment of pollution exposures. In our analysis, individuals were assigned an MSA-level average of 2001 and 2010 concentration estimates, as a proxy for lifetime exposure. Assigning lifetime exposure as the average of two annual estimates fails to account for the temporal complexity of component levels and composition. However, we found that intertemporal correlations for $PM_{2.5}$ components were consistently high ($r > 0.78$), which suggests that incorporating additional years of CTM exposure estimates would provide only marginal improvements in exposure accuracy. If anything, using the average of 2001 and 2010 concentrations resulted in conservative mortality risk estimates. For a thorough analysis on the influence of temporal exposure windows in the NHIS cohort, see Lefler et al.[31]

Additionally, NHIS public-use residential data included only the MSA of residence, which required assigning exposures at the MSA level. For this reason, along with the 36 km resolution in the CTM, we were unable to account for local variations in $PM_{2.5}$ components. This is particularly problematic for components with high spatial variability, such as EC.

Another limitation is that differences in component mortality associations could have been driven by statistical factors aside from toxicity. As previously mentioned, exposure modeling accuracy, observed variation, and component intercorrelation all affect the precision and magnitude of mortality risk estimates. While these factors vary between components, they are likely independent of the relative toxicity. Thus, differences in effect size and statistical significance could simply reflect varying statistical advantages, not differential mortality associations.

A final limitation is potential confounding from unobserved or inadequately controlled for risk factors. Specifically, unobserved characteristics such as dietary habits, physical activity, and climate could have resulted in spurious findings. Additionally, dynamic risk factors such as smoking status, BMI, income, and residence were reported only at the time of the survey, providing an imperfect measure of the lifetime pathway of these variables.

Notwithstanding these limitations, our findings suggest that there are differences in mortality associations across $PM_{2.5}$ species and sources. These differences appear to be driven by factors other than whether $PM_{2.5}$ is primary or secondary. After controlling for remaining $PM_{2.5}$, we found that the mortality association for EC was 10 times greater (per unit $\mu g/m^3$) than for total $PM_{2.5}$. Similarly, SOA and vehicle sources had significantly larger HRs in comparison to the remaining $PM_{2.5}$ mass (per unit $\mu g/m^3$). These findings suggest that targeted abatement strategies could be more beneficial to public health than simply reducing total $PM_{2.5}$. If corroborated in other studies, this analysis could help inform a targeted, efficient approach to reducing air pollution mortality.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.1c04176.

> Breakdown of cardiopulmonary mortality by ICD 10 codes, illustration of pollution exposures across NHIS surveyed MSAs, numeric single-pollutant hazard ratios (95% confidence intervals), numeric mass-adjusted hazard ratios (95% confidence intervals), numeric hazard ratios (95% confidence intervals) for primary and secondary species within $PM_{2.5}$ source, and measures of model fit (PDF)

■ AUTHOR INFORMATION

Corresponding Author

C. Arden Pope, III − *Department of Economics, Brigham Young University, Provo, Utah 84602, United States;* orcid.org/0000-0002-4239-6686; Phone: 801-422-2157; Email: cap3@byu.edu; Fax: 801-422-0194

Authors

Zachari A. Pond − *Department of Economics, Brigham Young University, Provo, Utah 84602, United States; Department of Agricultural and Resource Economics, University of California Berkeley, Berkeley, California 94720, United States;* orcid.org/0000-0002-6414-2441

Carlos S. Hernandez − *Department of Civil and Environmental Engineering, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213, United States*

Peter J. Adams − *Department of Civil and Environmental Engineering, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213, United States*

Spyros N. Pandis − *Department of Chemical Engineering, University of Patras, Patras 26504, Greece;* orcid.org/0000-0001-8085-9795

George R. Garcia − *Department of Economics, Brigham Young University, Provo, Utah 84602, United States; Stanford Law School, Palo Alto, California 94305, United States*

Allen L. Robinson − *Department of Mechanical Engineering, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213, United States;* orcid.org/0000-0002-1819-083X

Julian D. Marshall − *Department of Civil and Environmental Engineering, University of Washington, Seattle, Washington 98195, United States;* orcid.org/0000-0003-4087-1209

Richard Burnett − *Institute for Health Metrics and Evaluation, University of Washington, Seattle, Washington 98195, United States*

Ksakousti Skyllakou − *Institute of Chemical Engineering Sciences, Foundation for Research and Technology Hellas, Patras 26504, Greece*
Pablo Garcia Rivera − *Department of Chemical Engineering, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213, United States*
Eleni Karnezi − *Earth Sciences, Barcelona Supercomputing Center, Barcelona 08034, Spain*
Carver J. Coleman − *Department of Economics, Brigham Young University, Provo, Utah 84602, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.est.1c04176

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This publication was developed as part of the Center for Air, Climate, and Energy Solutions (CACES), which was supported under Assistance Agreement No. R835873 awarded by the U.S. Environmental Protection Agency. It has not been formally reviewed by the EPA. The views expressed in this document are solely those of the authors and do not necessarily reflect those of the Agency. EPA does not endorse any products or commercial services mentioned in this publication. We also acknowledge support from the European Union's Horizon 2020 Research and Innovation project REMEDIA under grant agreement No. 874753.

■ REFERENCES

(1) Murray, C. J.; Aravkin, A. Y.; Zheng, P.; Abbafati, C.; Abbas, K. M.; Abbasi-Kangevari, M.; Borzouei, S. Global burden of 87 risk factors in 204 countries and territories, 1990−2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **2020**, 1223−1249.
(2) Pope, C. A., III; Lefler, J. S.; Ezzati, M.; Higbee, J. D.; Marshall, J. D.; Kim, S. Y.; Burnett, R. T.; et al. Mortality risk and fine particulate air pollution in a large, representative cohort of US adults. *Environ. Health Perspect.* **2019**, *127*, 077007.
(3) Vodonos, A.; Awad, Y. A.; Schwartz, J. The concentration-response between long-term PM2.5 exposure and mortality; A meta-regression approach. *Environ. Res.* **2018**, *166*, 677−689.
(4) Chen, J.; Hoek, G. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. *Environ. Int.* **2020**, *143*, 105974.
(5) Thurston, G. D.; Burnett, R. T.; Turner, M. C.; Shi, Y.; Krewski, D.; Lall, R.; Pope, C. A., III; et al. Ischemic heart disease mortality and long-term exposure to source-related components of US fine particle air pollution. *Environ. Health Perspect.* **2016**, *124*, 785−794.
(6) Thakrar, S. K.; Balasubramanian, S.; Adams, P. J.; Azevedo, I. M.; Muller, N. Z.; Pandis, S. N.; Tessum, C. W.; et al. Reducing mortality from air pollution in the United States by targeting specific emission sources. *Environ. Sci. Technol. Lett.* **2020**, *7*, 639−645.
(7) Dockery, D. W.; Pope, C. A.; Xu, X.; Spengler, J. D.; Ware, J. H.; Fay, M. E.; Ferris, B. G.; Speizer, F. E. An association between air pollution and mortality in six US cities. *N. Engl. J. Med.* **1993**, *329*, 1753−1759.
(8) Pope, C. A.; Thun, M. J.; Namboodiri, M. M.; Dockery, D. W.; Evans, J. S.; Speizer, F. E.; Heath, C. W. Particulate air pollution as a predictor of mortality in a prospective study of US adults. *Am. J. Respir. Crit. Care Med.* **1995**, *151*, 669−674.
(9) Ostro, B.; Hu, J.; Goldberg, D.; Reynolds, P.; Hertz, A.; Bernstein, L.; Kleeman, M. J. Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California Teachers Study Cohort. *Environ. Health Perspect.* **2015**, *123*, 549−556.
(10) NCHS. *2014 National Health Interview Survey: Survey Description*. NHIS, Division of Health Interview Statistics; https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2014/srvydesc.pdf. (accessed 14 March 2021).
(11) NCHS. *National Health Interview Survey, Questionnaires, Datasets, and Related Documentation*. NHIS, Division of Health Interview Statistics; https://www.cdc.gov/nchs/nhis/1997-2018.htm. (accessed 14 March 2021).
(12) Skyllakou, K., Rivera, P. G., Dinkelacker, B., Karnezi, E., Kioutsioukis, I., Hernandez, C.; Pandis, S. N. (**2021**). Changes in $PM_{2.5}$ concentrations and their sources in the US from 1990 to 2010. *Atmospheric Chemistry and Physics* [preprint], in review; 1−34. DOI: 10.5194/acp-2021-495
(13) Karydis, V. A.; Tsimpidi, A. P.; Fountoukis, C.; Nenes, A.; Zavala, M.; Lei, W.; Molina, L. T.; Pandis, S. N. Simulating the fine and coarse inorganic particulate matter concentrations in a polluted megacity. *Atmos. Environ.* **2010**, *44*, 608−620.
(14) Murphy, B. N.; Pandis, S. N. Exploring summertime organic aerosol formation in the Eastern United States using a regional-scale budget approach and ambient measurements: Organic aerosol budget in the Eastern United States. *Journal of Geophysical Research: Atmospheres* **2010**, *115*, D24216.
(15) Tsimpidi, A. P.; Karydis, V. A.; Zavala, M.; Lei, W.; Molina, L.; Ulbrich, I. M.; Jimenez, J. L.; Pandis, S. N. Evaluation of the volatility basis-set approach for the simulation of organic aerosol formation in the Mexico City metropolitan area. *Atmos. Chem. Phys.* **2010**, *10*, 525−546.
(16) Posner, L. N.; Theodoritsi, G.; Robinson, A.; Yarwood, G.; Koo, B.; Morris, R.; Pandis, S. N.; et al. Simulation of fresh and chemically-aged biomass burning organic aerosol. *Atmos. Environ.* **2019**, *196*, 27−37.
(17) Wagstrom, K. M.; Pandis, S. N.; Yarwood, G.; Wilson, G. M.; Morris, R. E. Development and application of a computationally efficient particulate matter apportionment algorithm in a three-dimensional chemical transport model. *Atmos. Environ.* **2008**, *42*, 5650−5659.
(18) Wagstrom, K. M.; Pandis, S. N. Contribution of long range transport to local fine particulate matter concerns. *Atmos. Environ.* **2011**, *45*, 2730−2735.
(19) Wagstrom, K. M.; Pandis, S. N. Source−receptor relationships for fine particulate matter concentrations in the Eastern United States. *Atmos. Environ.* **2011**, *45*, 347−356.
(20) Skyllakou, K.; Murphy, B. N.; Megaritis, A. G.; Fountoukis, C.; Pandis, S. N. Contributions of local and regional sources to fine PM in the megacity of Paris. *Atmos. Chem. Phys.* **2014**, *14*, 2343−2352.
(21) Skyllakou, K.; Fountoukis, C.; Charalampidis, P.; Pandis, S. N. Volatility-resolved source apportionment of primary and secondary organic aerosol over Europe. *Atmos. Environ.* **2017**, *167*, 1−10.
(22) Donahue, N. M.; Robinson, A. L.; Stanier, C. O.; Pandis, S. N. Coupled partitioning, dilution, and chemical aging of semivolatile organics. *Environ. Sci. Technol.* **2006**, *40*, 2635−2643.
(23) Murphy, B. N.; Pandis, S. N. Simulating the formation of semivolatile primary and secondary organic aerosol in a regional chemical transport model. *Environ. Sci. Technol.* **2009**, *43*, 4722−4728.
(24) Robinson, A. L.; Donahue, N. M.; Shrivastava, M. K.; Weitkamp, E. A.; Sage, A. M.; Grieshop, A. P.; Lane, T. E.; Pierce, J. R.; Pandis, S. N. Rethinking organic aerosols: Semivolatile emissions and photochemical aging. *Science* **2007**, *315*, 1259−1262.
(25) Xing, J.; Pleim, J.; Mathur, R.; Pouliot, G.; Hogrefe, C.; Gan, C.-M.; Wei, C. Historical gaseous and primary aerosol emissions in the United States from 1990 to 2010. *Atmos. Chem. Phys.* **2013**, *13*, 7531−7549.
(26) Hernandez, C., Skyllakou, K., Garcia Rivera, P., Dinkelacker, B., Marshall, J., Pope, A.; Adams, P. (2021). *Bias corrections for speciated and source-resolved $PM_{2.5}$ chemical transport model simulations using a geographically weighted regression*. ChemRxiv [preprint]. DOI: 10.33774/chemrxiv-2021-h71p5.

(27) Brunsdon, C.; Fotheringham, A. S.; Charlton, M. E. Geographically weighted regression: A method for exploring spatial nonstationarity. *Geographical Analysis* **1996**, *28*, 281−298.
(28) van Donkelaar, A.; Martin, R. V.; Spurr, R. J. D.; Burnett, R. T. High-resolution satellite-derived PM2.5 from optimal estimation and geographically weighted regression over North America. *Environ. Sci. Technol.* **2015**, *49*, 10482−10491.
(29) van Donkelaar, A.; Martin, R. V.; Li, C.; Burnett, R. T. Regional estimates of chemical composition of fine particulate matter using a combined geoscience-statistical method with information from satellites, models, and monitors. *Environ. Sci. Technol.* **2019**, *53*, 2595−2611.
(30) Kim, S. Y.; Bechle, M.; Hankey, S.; Sheppard, L.; Szpiro, A. A.; Marshall, J. D. Concentrations of criteria pollutants in the contiguous U.S., 1979 − 2015: Role of prediction model parsimony in integrated empirical geographic regression. *PLoS One* **2020**, *15*, e0228535.
(31) Lefler, J. S.; Higbee, J. D.; Burnett, R. T.; Ezzati, M.; Coleman, N. C.; Mann, D. D.; Pope, C. A.; et al. Air pollution and mortality in a large, representative US cohort: multiple-pollutant analyses, and spatial and temporal decompositions. *Environ. Health* **2019**, *18*, 101.
(32) Smith, K. R.; Jerrett, M.; Anderson, H. R.; Burnett, R. T.; Stone, V.; Derwent, R.; Pope, C. A., III; et al. Public health benefits of strategies to reduce greenhouse-gas emissions: health implications of short-lived greenhouse pollutants. *Lancet* **2009**, *374*, 2091−2103.
(33) Hvidtfeldt, U. A.; Sørensen, M.; Geels, C.; Ketzel, M.; Khan, J.; Tjønneland, A.; Overvad, K.; Brandt, J.; Raaschou-Nielsen, O. Long-term residential exposure to PM2.5, PM10, black carbon, NO2, and ozone and mortality in a Danish cohort. *Environ. Int.* **2019**, *123*, 265−272.
(34) Kelly, F. J.; Fussell, J. C. Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. *Atmos. Environ.* **2012**, *60*, 504−526.
(35) Cao, J.; Xu, H.; Xu, Q.; Chen, B.; Kan, H. Fine particulate matter constituents and cardiopulmonary mortality in a heavily polluted Chinese city. *Environ. Health Perspect.* **2012**, *120*, 373−378.
(36) Beelen, R.; Hoek, G.; Raaschou-Nielsen, O.; Stafoggia, M.; Andersen, Z. J.; Weinmayr, G.; Nieuwenhuijsen, M. J.; et al. Natural-cause mortality and long-term exposure to particle components: an analysis of 19 European cohorts within the multi-center ESCAPE project. *Environ. Health Perspect. Suppl.* **2013**, *2013*, 4186.
(37) Pope, C. A., III; Burnett, R. T.; Thun, M. J.; Calle, E. E.; Krewski, D.; Ito, K.; Thurston, G. D. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* **2002**, *287*, 1132−1141.
(38) Schlesinger, R. B.; Cassee, F. Atmospheric secondary inorganic particulate matter: the toxicological perspective as a basis for health effects risk assessment. *Inhalation Toxicol.* **2003**, *15*, 197−235.
(39) HEI Panel on the Health Effects of Traffic-Related Air Pollution (2010). *Traffic-related air pollution: A critical review of the literature on emissions, exposure, and health effects*. HEI Special Report 17.
(40) Ostro, B.; Tobias, A.; Querol, X.; Alastuey, A.; Amato, F.; Pey, J.; Perez, N.; Sunyer, J. The effects of particulate matter sources on daily mortality: A case-crossover study of Barcelona, Spain. *Environ. Health Perspect.* **2011**, *119*, 1781−1787.
(41) Laden, F.; Neas, L. M.; Dockery, D. W.; Schwartz, J. Association of fine particulate matter from different sources with daily mortality in six US cities. *Environ. Health Perspect.* **2000**, *108*, 941−947.
(42) Rich, D. Q.; Zhang, W.; Lin, S.; Squizzato, S.; Thurston, S. W.; van Wijngaarden, E.; Croft, D.; Masiol, M.; Hopke, P. K. Triggering of cardiovascular hospital admissions by source specific fine particle concentrations in urban centers of New York State. *Environ. Int.* **2019**, *126*, 387−394.
(43) Croft, D. P.; Zhang, W.; Lin, S.; Thurston, S. W.; Hopke, P. K.; van Wijngaarden, E.; Rich, D. Q.; et al. Associations between source-specific particulate matter and respiratory infections in New York State adults. *Environ. Sci. Technol.* **2020**, *54*, 975−984.

https://doi.org/10.1021/acs.est.1c04176
Environ. Sci. Technol. 2022, 56, 7214−7223